REMARKS

Finality of Office Action

In response to the Final Office Action, Applicant respectfully requests that the Examiner enter the foregoing amendments and consider the following remarks because the claims are in condition for allowance. In the alternative, Applicant requests that the claims amendments be entered because they better place the claims in condition for an appeal.

Election/Restrictions

The Office Action stated that a complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action. Accordingly, claims 10-18 are canceled herein without prejudice, waiver, or disclaimer. Applicant takes this action merely to reduce the number of disputed issues and to facilitate early allowance and issuance of other claims in the present application. Applicant reserves the right to pursue the subject matter of these canceled claims in a continuing application, if Applicant so chooses, and does not intend to dedicate any of the canceled subject matter to the public.

Withdrawn Rejections

Applicant thanks the Examiner for carefully considering Applicant's claim amendments and arguments submitted on July 16, 2004, and for withdrawing rejections made in the previous Office Action.

Maintained Rejections

Double-Patenting

In response to the double patenting rejection, Applicant submits herewith a terminal disclaimer pursuant to 37 C.F.R. §1.321(c). Applicant has submitted the terminal disclaimer solely for the reason of advancing prosecution of the application, without conceding that the double patenting rejection is properly based. In filing the terminal disclaimer, Applicant relies upon the rulings of the Federal Circuit that the filing of such a terminal disclaimer does not act as an admission, acquiescence, or estoppel on the merits of the obviousness issue. *See, e.g., Quad Envtl. Tech v. Union Sanitary Dist.*, 946 F.2d 870, 874-875 (Fed. Cir. 1991); and *Ortho Pharm. Corp. v. Smith*, 959 F.2d 936, 941-942 (Fed. Cir. 1992).

Rejections Under 35 U.S.C. 102(e)

(a) Claims 1 and 25-34 are rejected under 35 U.S.C. 102(e) as being anticipated by *Vivekananda et al.* (U.S. Patent No. 6,569,630). Applicant traverses this rejection for at least the reason that *Vivekananda* does not teach or suggest at least the step of claim 1 of "providing a collection of nucleotides ..., the collection including at least a first complementary nucleotide that hybridizes with a first residue within the first sequence element on the template strand and a second complementary nucleotide that hybridizes with a second residue within the second sequence element on the template strand, wherein the first and second residues are complementary to one another but the first and second nucleotides have a reduced ability to form a stable hydrogen bonded base pair." In the Office Action, the Examiner responds to Applicant's previous arguments by asserting the following:

> In columns 20-24, 29-31, Vivekananda et al. teach the synthesis of nucleic acid ligands that contain modified nucleotides that render intra-strand, complementary nucleotides with a reduced ability to form stable hydrogen bonded base pairs.

Office Action at 3. Applicant respectfully traverses. For example, in cols. 20-21, *Vivekananda* simply provides a laundry list of various modified nucleotide bases, but still does not provide for the step of claim 1 recited above.

In addition, the Office states that "the fact that aptamers are a preferred embodiment does not preclude *Vivekananda* as prior art of the instantly claimed invention." *Office Action* at 3. Applicant traverses because the feature of claim 1 recited above is not taught by the aptamer embodiment of *Vivekananda*. Indeed, at the cols. 29-31 of *Vivekananda* cited by the Office, the nucleic acid ligands to be used are consistently referred to as aptamers. *See, e.g.*, col. 29, lines 32-33, 39, 56-59, 63-67 and col. 30, lines 1-3. *Vivekananda* describe their nucleic acids as aptamers, that is "a nucleic acid that binds to another molecule ('target' as defined below). This binding interaction does not encompass standard nucleic acid/nucleic acid hydrogen bond formation ...." *Vivekananda*, col. 8, lines 27-33 (emphasis added). No where does *Vivekananda* teach or suggest first and second residues that are complementary to one another but have a reduced ability to form a stable hydrogen bonded base pair, as recited in claim 1. In addition, *Vivekananda* does not teach or suggest an unstructured nucleic acid in which two complementary nucleotides of the unstructured nucleic acid do not form an intramolecular base pair, as recited in claim 1. For at least these reasons, the rejection is misplaced and should be withdrawn.

(b) Claims 1 and 25-35 are rejected under 35 U.S.C. 102(e) as being anticipated by *Kutyavin et al.* (U.S. 5,912,340). Applicant respectfully traverses for at least the reason that *Kutyavin* does not teach or suggest at least ***any*** of the steps of claim 1.

Attached as Exhibit "A" are three schemes that Applicant has developed to help elucidate the present claims in view of the prior art and demonstrate the novelty and nonobviousness of the claims in view of the prior art. As illustrated in Scheme A, prior to *Kutyavin*, strand invasion of double-stranded DNA or RNA was typically accomplished via the incorporation of a single strand of an oligonucleotide into the double-stranded DNA or RNA. As demonstrated in Scheme B, *Kutyavin* discloses ***a matched set of oligonucleotides*** containing modified nucleotides, where each member of the set is able to hybridize with a complementary strand in a ***duplex nucleic acid molecule***, but is unable to hybridize with the other member of the matched set. Support for the characterization of the teachings of *Kutyavin* as illustrated in Scheme B can be found in at least the following passages of *Kutyavin*:

> In accordance with the present invention ***a matched pair of oligonucleotides*** (ODNs) are provided where each member of the pair is complementary or substantially complementary in the Watson Crick sense to a ***target duplex sequence***.... The ODNS of the invention... form substantially stable hybrids with the target sequence ***in each strand of duplex nucleic acid.***
>
> The ODNs of the present invention are termed Selective Binding Complementary (SBC) ODNs....
>
> [A] key feature of the SBC ODNs of the present invention is that ***each*** one of a matched pair of the SBC ODNs is complementary, or substantially complementary, to one target sequence in ***duplex*** nucleic acid wherein the target sequences are themselves complementary or substantially complementary to one another, and each one of the matched pair of SBC ODNs forms a stable hydrogen bonded hybrid with one strand of the target sequence.... ***Thus, the SBC ODNs are not hybridized to one another but they readily hybridize, especially ... when the target is in long double stranded DNA, with both strands of the target sequence.***

Kutyavin at col. 1, lines 39-67 and col. 2, lines 14-31 (emphasis added). In addition, *Kutyavin* refers to the modified SBC nucleotides at the following passage:

> ***A sufficient number of the modified SBC nucleotides are incorporated such that complementary positions in both SBC ODNS are modified into a matched pair of SBC ODNs of the present invention so that the pair of the matched set does not form a stable hybrid***.... It is not necessary to replace

> each natural nucleotide of the ODN with a modified SBC nucleotide in order to accomplish this. Both members of the matched pair are however complementary to a target sequence in double stranded or duplex nucleic acid, where the two strands or parts of the target duplex are themselves complementary or substantially complementary to one another. As it is described in more detail below, an important use of the SBC ODNs of the present invention is hybridization with secondary structure of mRNA wherein the mRNA itself forms a duplex, such as in hairpin loops.... The general concept of double stranded DNA and of secondary structure in mRNA and ribosomal RNA is covered in this description by the term "duplex nucleic acid".

Kutyavin at col. 4, lines 39-67 (emphasis added). In this passage, *Kutyavin* is referring to the formation of ***probes*** in, for example, a hybridization assay. In contrast, as recited in claim 1, the targets themselves are synthesized.

As illustrated in Scheme C, one embodiment of claim 1 includes providing a nucleic acid template and providing nucleotides that have certain characteristics[1], such that when the nucleotides are polymerized to form an unstructured nucleic acid, the nucleotides do not form an ***intramolecular*** base pair. Support for the illustration in Scheme C can be found in the specification at least at FIGs. 8A-8C and their attendant descriptions in the originally filed specification. This is novel and nonobvious in view of *Kutyavin*. Applicant discovered the following:

> [T]here is a correlation between the predicted stability of the polynucleotide's secondary structure and its efficiency as a target in the single-base extension reaction. HP28 is a more efficient target than HP26 which, in turn, is a more efficient target than HP21 suggesting that ***intramolecular target structures near a primer binding site can effect the polymerase extension efficiency at that site***. Thus because this same trend is exaggerated for the D [2-amino-2'-deoxyadenosine-5'-triphosphate (dDTP)] and S [2-thiothymidine-5-triphosphate (2-thioTTP)]-containing polynucleotides, the results support the conclusion that the modifications do indeed alter the secondary structure of the polynucleotide targets. ... ***[T]hese results clearly demonstrate that incorporating the 2-aminoadenosine and 2-thiothymidine nucleotide pair into a polynucleotide sequence increases the utility of the polynucleotide in hybridization-based assays.***

Specification at last paragraph. Thus, not all the steps/features of claim 1 are taught or suggested by *Kutyavin*.

[1] Note that Scheme C uses the term "modified nucleotides." This term is merely for purposes of illustrating the concepts of Scheme C, as one embodiment, and not intended to limit the scope of claim 1. The term "collection of nucleotides" in claim 1 should be given its full scope and meaning in accordance with the specification as originally filed.

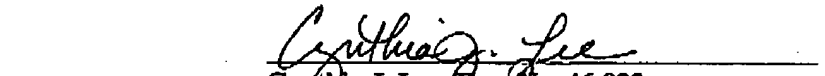
For at least this reason, Applicant therefore respectfully requests that the rejection of claim 1 be withdrawn.

If independent claim 1 is allowable over the prior art of record, then its respective dependent claims 25-35 are also allowable as a matter of law, because these dependent claims contain all features/elements/steps of their respective independent claim. Additionally and notwithstanding the foregoing reasons for the allowability of claim 1, the dependent claims recite further features and/or combinations of features, as apparent by examination of the claims themselves, that are patentably distinct from the prior art of record. Hence, there are other reasons why these dependent claims are allowable over *Vivekananda* and *Kutyavin*.

CONCLUSION

In light of the foregoing amendments and for at least the reasons set forth above, Applicant respectfully submits that all rejections have been traversed, rendered moot, and/or accommodated, and that the now pending claims 1 and 25-35 are in condition for allowance. Favorable reconsideration and allowance of the present application and all pending claims are hereby courteously requested. If, in the opinion of the Examiner, a telephone conference would expedite the examination of this matter, the Examiner is invited to call the undersigned agent at (770) 933-9500.

Respectfully submitted,



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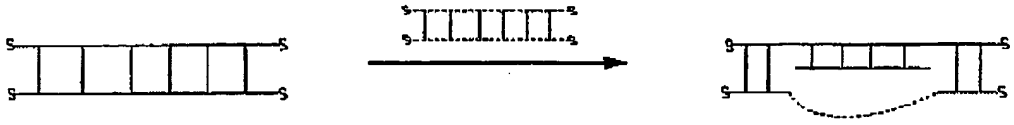
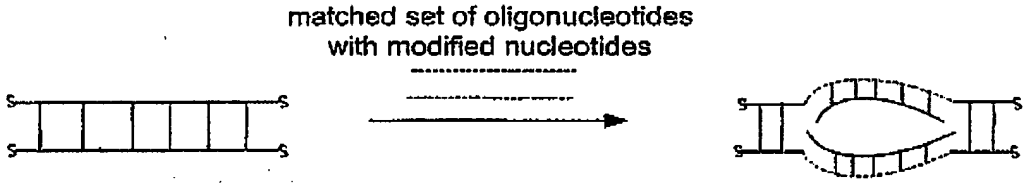
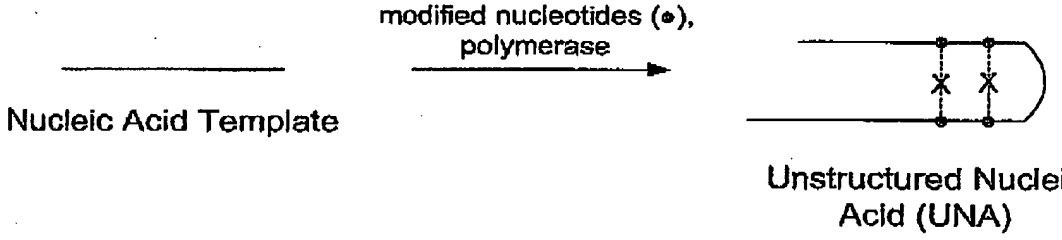


SCHEME A - PRIOR TO KUTYAVIN



SCHEME B - KUTYAVIN



SCHEME C - ONE EMBODIMENT OF CLAIM 1

EXHIBIT A
PAGE 1 OF 1

CERTIFICATE OF FACSIMILE

I hereby certify that this correspondence (16 pages) is being faxed to (571) 273-8300; Attn: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

on August 15, 2005.

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Examiner: **Zara, Jane J.**

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For: **Method of Producing Nucleic Acid Molecules with Reduced Secondary Structure**

The following is a list of documents enclosed:

Amendment Transmittal Page
Terminal Disclaimer
Response
Exhibit A to Response
Authorization to charge Deposit Account No. 50-1078 the amount of $130.00 for the Terminal Disclaimer fee;
Certificate of Facsimile

Further, the Commissioner is authorized to charge Deposit Account No. 20-0778 for any additional fees required. The Commissioner is requested to credit any excess fee paid to Deposit Account No. 20-0778.